Bevacizumab plus hypofractionated radiotherapy versus radiotherapy alone in elderly patients with glioblastoma: the randomized, open-label, phase II ARTE trial

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Abstract: Background The addition of bevacizumab to temozolomide-based chemoradiotherapy (TMZ/RT → TMZ) did not prolong overall survival (OS) in patients with newly diagnosed glioblastoma in phase III trials. Elderly and frail patients are underrepresented in clinical trials, but early reports suggested preferential benefit in this population. Patients and methods ARTE was a 2 : 1 randomized, multicenter, open-label, non-comparative phase II trial of hypofractionated RT (40 Gy in 15 fractions) with bevacizumab (10 mg/kg×14 days) (arm A, N = 50) or without bevacizumab (arm B, N = 25) in patients with newly diagnosed glioblastoma aged 65 years. The primary objective was to obtain evidence for prolongation of median OS by the addition of bevacizumab to RT. Response was assessed by RANO criteria. Quality of life (QoL) was monitored by the EORTC QLQ-C30/BN20 modules. Exploratory studies included molecular subtyping by 450k whole methylome and gene expression analyses. Results Median PFS was longer in arm A than in arm B (7.6 and 4.8 months, P = 0.003), but OS was similar (12.1 and 12.2 months, P = 0.77). Clinical deterioration was delayed and more patients came off steroids in arm A. Prolonged PFS in arm A was confined to tumors with the receptor tyrosine kinase (RTK) I methylation subtype (HR 0.25, P = 0.014) and proneural gene expression (HR 0.29, P = 0.025). In a Cox model of OS controlling for established prognostic factors, associations with more favorable outcome were identified for age <70 years (HR 0.52, P = 0.018) and Karnofsky performance score 90%-100% (HR 0.51, P = 0.026). Including molecular subtypes into that model identified an association of the RTK II gene methylation subtype with inferior OS (HR 1.73, P = 0.076). Conclusion Efficacy outcomes and exploratory analyses of ARTE do not support the hypothesis that the addition of bevacizumab to RT generally prolongs survival in elderly glioblastoma patients. Molecular biomarkers may identify patients with preferential benefit from bevacizumab. Clinical trial registration number NCT01443676.

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Bevacizumab plus hypofractionated radiotherapy versus radiotherapy alone in elderly patients with glioblastoma: the randomized, open-label, phase II ARTE trial

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Abstract

Background: The addition of bevacizumab to temozolomide-based chemoradiotherapy (TMZ/RT→TMZ) did not prolong overall survival (OS) in patients with newly diagnosed glioblastoma in phase III trials. Elderly and frail patients are underrepresented in clinical trials, but early reports suggested preferential benefit in this population.

Patients and Methods: ARTE was a 2:1 randomized, multi-center, open-label, non-comparative phase II trial of hypofractionated RT (40 Gy in 15 fractions) with bevacizumab (10 mg/kg x 14 days) (arm A, *N=50*) or without bevacizumab (arm B, *N=25*) in patients with newly diagnosed glioblastoma aged ≥65 years. The primary objective was to obtain evidence for prolongation of median OS by the addition of bevacizumab to RT. Response was assessed by RANO criteria. Quality of life (QoL) was monitored by the EORTC QLQ-C30/BN20 modules. Exploratory studies included molecular subtyping by 450k whole methylome and gene expression analyses.

Results: Median PFS was longer in arm A than in arm B (7.6 and 4.8 months, *P=0.003*), but OS was similar (12.1 and 12.2 months, *P=0.77*). Clinical deterioration was delayed and more patients came off steroids in arm A. Prolonged PFS in arm A was confined to tumors with the receptor tyrosine kinase (RTK) I methylation subtype (HR 0.25, *P=0.014*) and proneural gene expression (HR 0.29, *P=0.025*). In a Cox model of OS controlling for established prognostic factors, associations with more favorable outcome were identified for age <70 years (HR 0.52, *P=0.018*) and Karnofsky performance score (KPS) 90-100% (HR 0.51, *P=0.026*). Including molecular subtypes into that model identified an association of the RTK II gene methylation subtype with inferior OS (HR 1.73, *P=0.076*).

Conclusion: Efficacy outcomes and exploratory analyses of ARTE do not support the hypothesis that the addition of bevacizumab to RT generally prolongs survival in

elderly glioblastoma patients. Molecular biomarkers may identify patients with preferential benefit from bevacizumab.

Clinical trial registration number: NCT01443676

Key message

The randomized, open-label, phase II ARTE trial explored the efficacy of bevacizumab in combination with hypofractionated radiotherapy in patients with newly diagnosed glioblastoma aged >65 years. Median progression-free survival was 2.8 months longer in the bevacizumab arm, but overall survival was similar. The notion of preferential benefit from bevacizumab in elderly patients was not confirmed.

Introduction

Almost 50% of all patients with glioblastoma are older than 65 years, less than 20% of these survive the first year [1]. Many elderly patients with glioblastoma are deemed too frail to tolerate combined post-operative temozolomide chemoradiotherapy (TMZ/RT→TMZ), [2, 3] rendering monotherapy regimens of hypofractionated RT [4] or TMZ alone preferred treatment options for some of these patients [5-7].
The vascular endothelial growth factor (VEGF)-targeting antibody bevacizumab (Avastin™) was considered an optimal candidate drug to improve overall survival (OS) of elderly glioblastoma patients based on results of early, uncontrolled clinical reports that suggested preferential benefit from bevacizumab in frail and elderly patients (Note S1). Yet, bevacizumab failed to prolong overall survival (OS) in two phase III trials and there was only a trend for more benefit from bevacizumab in patients with unfavorable prognostic factors, although frail elderly patients were underrepresented in these trials since being eligible for TMZ/RT→TMZ was an inclusion criterion in both trials [8, 9].

Patients and Methods

Study design

ARTE (NCT01443676) was designed as a 2-arm, randomized, non-comparative, open-label phase II trial. The primary objective was to determine the efficacy and tolerability of the combination of bevacizumab and radiotherapy in elderly patients with newly diagnosed glioblastoma. The primary endpoint was median OS. Major inclusion criteria were: age 65 years or older, newly diagnosed supratentorial

glioblastoma, eligible for first infusion of bevacizumab ≥ 28 and ≤ 49 days after surgery for glioblastoma, Karnofsky performance score (KPS) of 60 or more, stable or decreasing corticosteroid dose within 5 days prior to enrolment, availability of paraffin-embedded tissue for central pathology review and determination of O^6-methylguanine DNA methyltransferase (*MGMT)* promoter methylation status, and adequate hematological, renal and liver function. An amendment (11/2013) requested the absence of *MGMT* promoter methylation when it became clear that *MGMT* promoter methylation predicted larger benefit from temozolomide alone than from RT alone in patients with glioblastoma aged ≥65 years [5, 6]. All patients gave written informed consent, and the study was approved by the local ethical committees and competent authorities (KEK-ZH No. 2011-0135).

Central pathology review and molecular analyses

Histological diagnoses were reviewed centrally (E.R.) based on the 2007 World Health Organization (WHO) classification [10]. Molecular assessments included *IDH* mutation, *MGMT* promoter methylation, genome-wide CpG methylation and nCounter gene expression arrays (Note S2).

Study treatment, assessments and endpoints

Patients were allocated to treatment arms using a web-based randomization system without stratification in a 2:1 distribution. RT was administered to the gross tumor volume plus a 2 cm margin over 3 weeks, in 15 fractions of 2.66 Gy, to a total 40.0 Gy. Bevacizumab was administered intravenously at 10 mg/kg bodyweight every two weeks. Dose delays were foreseen for adverse reactions associated with bevacizumab that were considered likely to evolve into serious or life-threatening

events. Bevacizumab was stopped for disease progression or unacceptable toxicity, including life-threatening events or subjective patient-related factors. Details on clinical assessments and endpoints are provided in Note S3.

Statistical analyses

The initial sample size was 40 patients for arm A and 20 patients for arm B. Sample size calculations were based on the experimental arm only for the null hypothesis that, based on NOA-08 [6], median OS was 10 months, for an approximate 80% power to detect an improvement of 2 months using a two-sided alpha level of 10%. Per amendment, the study design was modified to aim for enrollment of 60 patients with tumors without *MGMT* promoter methylation. Details on the applied statistical tests are summarized in Note S4.

Results

Patient characteristics

At 9 sites in Switzerland, 75 patients aged 65 years or older were randomized from 3/2013 to 8/2015 (Figure S1). Arms A and B were overall well balanced (Table 1). More patients in arm A had cognitive impairment (42% versus 15%, *P=0.032*). The *MGMT* promoter methylation status was available for 72 patients (96%), 55 tumors (76%) had an unmethylated *MGMT* promoter. Genome-wide methylation arrays revealed 16 tumors (28%) with receptor tyrosine kinase (RTK) I, 23 tumors (40%) with RTK II and 16 tumors (28%) with mesenchymal (MES) methylation patterns. Gene expression subtyping revealed 15 proneural (PN) (29%), 19 classical (CL) (37%), and 17 MES (33%) glioblastomas. At the time of databank closure (19 August

2016), 74 deaths were documented, of which 70 were attributed to tumor progression, 1 was of unknown cause, and 3 from pulmonary embolism, myocardial infarction and gastrointestinal perforation, respectively. One patient was still on study treatment, no patient was lost to follow-up for OS.

Safety and tolerability

Adverse events are summarized in Table S1. Grade 3-5 events were overall infrequent. More adverse events occurred in arm A than in arm B, but there was also a longer treatment period in arm A. The rate of thromboembolic events was similar in both groups (19% versus 20%), but more severe and life-threatening thromboembolic events occurred in arm A (16% versus 8%), including one death each from pulmonary embolism and myocardial infarction. Bevacizumab was discontinued for reasons other than progression in 4 patients, including death in 1 patient, pulmonary embolism in 2 patients and withdrawal of consent in 1 patient.

Efficacy estimates by treatment arm

The median time from surgery to randomization was 25 days (range 16-41) in arm A and 24 days (range 16-37) in arm B (p=0.60). Forty-seven of 50 patients in arm A and 23 of 25 patients in arm B completed the intended dose of 40 Gy of hypofractionated RT. The median number of bevacizumab administrations in arm A was 12 (range 0-86). Median PFS was 7.6 months in arm A and 4.8 months in arm B (Figure 1A, Table S2, *P=0.003*) and PFS at 6 months (PFS6) was 78% and 28% in arms A and B (Table S2, *P<0.001*). Median PFS was also more favorable in arm A when analyses were restricted to the per protocol population, i.e., to patients with tumors with an unmethylated *MGMT* promoter and confirmation of the histopathological diagnosis by central neuropathology review (Figure S3). Median

PFS in the per protocol population was 7.6 months in arm A and 4.7 months in arm B (Table S3, *P=0.071*). Twenty-four of 48 patients in arm A (50%), but 18 of 25 patients (72%) in arm B received any salvage therapy at progression (*P=0.071*). Median OS in the intent to treat population was 12.1 months in arm A and 12.2 months in arm B (Figure 1B, Table S2, *P=0.77*), and survival rates at 12 months (OS12) were 54% and 56% in arms A and B (Table S2, *P=0.85*). Similarly, no apparent benefit from bevacizumab with respect to OS emerged in the per protocol population (Table S3).

Central radiology review and response assessment

Serial MRI of 66 patients were available for post-hoc central review. At study entry, all but two patients, both from arm A, had contrast-enhancing lesions, which qualified for measurable disease. Response measures were balanced between treatment arms (*P=0.15*, Table S4). The locally determined time point of progression was centrally confirmed in 54 patients. It was antedated in arm A by 1 scan in 8 patients, 2 scans in 2 patients and 4 scans in 1 patient, all of which qualified for pseudoresponse by RANO criteria because of progression on T2-FLAIR sequences. Among patients from arm B, progression was antedated 1 scan in 1 patient. Central review confirmed longer PFS in arm A than in arm B (median PFS 7.0 versus 4.7 months, *P=0.029*).

Quality of life, cognitive functioning and steroid use

Adherence of the study population to quality of life measurements at each scheduled study visit was in the range of 65-96% in arm A and 44-80% in arm B. Median deterioration-free survival from baseline was 5.7 months in arm A and 2.8 months in arm B (Figure 1C, Table S3, *P<0.001*). Prior to progression, no differences were detected for individual scales in a generalized linear mixed model, except for less

favorable values in arm A for global health (*P=0.048*) and pain (*P=0.027*) (Figure 1D).

Cognitive functioning was additionally assessed by serial MMSE. It remained stable prior to progression in both groups and no difference between arms was detected at individual visits (Figure 1E), or in a linear regression model (*P=0.43* for differences in slopes). Six individuals with a decline in MMSE of 5 points or more prior to progression were identified, all of which were treated in arm A. Two of these six patients qualified for pseudoresponse by RANO.

Among 34 patients who were on steroids at study entry, 21 of 22 patients (95%) in arm A and 8 of 12 patients (66%) in arm B came off steroids prior to progression (*P=0.024*). The median time on steroids from study entry was 1.6 months in arm A and 2.6 months in arm B (*P=0.38*) (censoring patients at progression).

Exploratory analyses of treatment effects

Treatment effects on PFS were noted throughout most clinically defined subgroups and were pronounced in patients with poor general condition at baseline (KPS $\leq$80%, HR 0.16, 95% CI 0.06-0.45, *P<0.001*) and in patients with cognitive impairment at baseline (MMSE <27 points, HR 0.08, 95% CI 0.02-0.41, *P=0.002*). In contrast, no improved PFS was noted in patients with better cognitive functioning (MMSE $\geq$27, HR 0.85, 95% CI 0.42-1.72, *P=0.66*, Figure S3).

Exploratory analyses of treatment effects with respect to OS identified no subgroup with benefit from bevacizumab, albeit a tendency to prolonged OS was noted in patients with poor general condition (KPS 60-80%, HR 0.55, 95% CI 0.24-1.24, *P=0.15*) and patients who did not receive any second line therapy (HR 0.44, 95% CI 0.17-1.15, *P=0.092*, Figure S3).

Utilizing median PFS or OS as a cut-off, receiver operating characteristics analyses failed to identify prognostic cut-offs for baseline planimetric estimates of contrast enhancement on T1-weighted images, or for tumor sizes on T2-weighted images, including separate analysis of the entire study cohort, arm A or arm B (data not shown).

Clinical characteristics and outcome by gene methylation and gene expression

Unsupervised clustering of gene methylation similarities reflected the methylation classifier-based assignment of glioblastoma subtypes (Figure 2A). Groups defined by methylation subtypes did not differ with respect to established prognostic factors, including age (*P=0.44*), KPS (*P=0.80*), steroid intake at study entry (*P=0.41*) or MGMT promoter methylation (*P=0.91*) and no differences in PFS or OS were detected (Figure S4).

Longer PFS in arm A than in arm B was detected solely in the subgroup of RTK I glioblastomas (HR 0.25, 95% CI 0.07-0.82, *P=0.014*, Figures 2B, S3 and S4) and there was a trend towards a higher rate of radiographic complete responses of RTK I compared to RTK II or MES glioblastomas (Table S4). No gene methylation subtype with prolonged OS in arm A versus arm B was identified (Figures 2C, S3 and S4).

There was an association of methylation subtypes with gene expression subtypes (*P=0.011*), including RTK I methylation in 57% of PN, RTK II methylation in 73% of CL and MES methylation in 53% of glioblastomas with MES gene expression (Figure 2A). No differences in PFS and OS were detected between gene expression subtypes (Figure S5). PFS was specifically longer among bevacizumab-treated patients with IDH wildtype PN glioblastomas (HR 0.29, 95% CI 0.08-0.98, *P=0.025*) (Figures 2D, S3 and S5). No gene expression subtype with differences in OS between treatment arms was identified (Figures 2E, S3 and S5). Outcome analyses

of the MES gene expression subtype were precluded by imbalance between treatment arms (Table 1, Figure S5).

Multivariate modeling of outcome

Cox proportional hazards modeling for PFS revealed treatment with bevacizumab and higher KPS as relevant prognostic factors, whereas no role for age, steroid intake at study entry or *MGMT* promoter methylation emerged (Table 2). Applying the same model to OS revealed age and KPS as relevant prognostic factors (Table 2). Univariate analyses are summarized in Table S5. Inclusion of gene methylation and gene expression subtypes into this model as additional single variables identified an association of the RTK II subtype with inferior PFS and OS (Table S6).

We also considered the possibility that second line treatment masked effects from study treatment on OS. However, in our model the inclusion of any salvage therapy versus best supportive care at recurrence did not render treatment arm a prognostic factor (HR 1.01, 95% CI 0.55-1.87, *P=0.96*), and neither were surgery at recurrence (HR for arm A versus arm B 0.89, 95% CI 0.34-2.30, *P=0.80*), or cross-over to receive bevacizumab at recurrence in arm B (HR for arm A versus arm B 0.63, 95% CI 0.29-1.32, *P=0.22*) prognostic. In arm B, 13 patients (52%) received bevacizumab at first or second recurrence, including two patients (8%) who received bevacizumab at first and second recurrence (Figure S1).

Discussion

The ARTE trial was designed to provide evidence for a benefit from first-line bevacizumab anti-angiogenic therapy when added to RT in elderly glioblastoma

patients considered non-eligible for combined modality treatment, based on standards of care when the trial was initiated [11]. The amendment of the trial to include only patients with an unmethylated *MGMT* promoter was motivated ethically when it became clear that temozolomide and not RT was the preferred first-line monotherapy for elderly glioblastoma patients with a methylated *MGMT* promoter considered non-eligible for combined modality treatment [5, 6]. Given that benefit from RT is not associated with absence or presence of *MGMT* promoter methylation in this patient population, we focused our analyses on the intention-to-treat population.

We found indeed a small increase in OS of approximately 2 months over the historical benchmark of the NOA-08 trial, but a similar increase was also seen in the patients treated with RT alone, suggesting an effect of patient selection or improved standards of care with time [12], although cross-over to receive bevacizumab in arm B contributing to OS cannot be ruled out. Overall the outcome data reported in ARTE compare well with contemporary patient populations (Table S7). That the addition of bevacizumab increased PFS, but apparently not OS is consistent with the phase III trials concluded while ARTE was ongoing [8, 9]. The benefit in PFS with bevacizumab according to central review was consistent with the benefit according to investigator assessment, albeit the timepoint of progression was antedated in 22% of patients in arm A due to more rigorous application of imaging criteria.

Early uncontrolled reports of bevacizumab therapy in glioblastoma patients suggested that benefit may be pronounced in elderly and frail patients [13-15]. Accordingly, an OS benefit from bevacizumab in patients who did not qualify for second line therapy was reported from secondary analyses of the AVAGlio trial [16]. We also noted a tendency towards prolonged OS in patients with lower KPS and in

patients who did not receive further treatment at tumor progression, albeit these subgroup analyses suffer from the lack of statistical power.

In line with reports from the AVAGlio trial [8, 17], patient-reported quality of life was maintained under bevacizumab at least until progression and more patients came off steroids with bevacizumab. In contrast, an association of bevacizumab treatment with inferior QoL and worse cognitive functioning was reported from the RTOG-0825 trial [9], fostering speculation on putative neurotoxicity of bevacizumab. In the ARTE trial, bevacizumab was overall well tolerated, but indeed more neuropsychiatric adverse events and cognitive decline prior to progression were noted in arm A. Although neurotoxicity from bevacizumab cannot be ruled out, other causes potentially contributing to cognitive impairment in individual patients in arm A included the prolonged treatment period, imbalances in cognitive functioning at baseline and unrecognized tumor progression, as determined by the post-hoc radiology review. The largest fraction of adverse events in both treatment arms were classified as other neurologic events, comprising mostly sensorimotor symptoms likely related to tumor burden.

Secondary analyses of outcome measures also included stratification by molecular markers. Genome-wide analysis of gene methylation identified an association of the RTK I methylation subtype and the proneural gene expression subtype with PFS benefit from bevacizumab. Although sample size was small, these results confirm the previously reported link of preferential benefit from bevacizumab in patients with tumors with proneural gene expression pattern [18]. This may provide an important path forward for patient selection in future clinical trials exploring VEGF-targeted therapies.

In conclusion, ARTE did not confirm the hypothesis that the combination of

bevacizumab with hypofractionated RT prolongs OS in elderly glioblastoma patients, but exploratory analyses yielded novel molecular genetic and imaging biomarkers that may help to enrich patient populations for future trials on novel anti-VEGF compounds.

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Disclosures

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Figure Legends

Figure 1. **Clinical outcome by treatment arm.** *A, B:* Progression-free survival *(A)* and overall survival *(B)* were analyzed in the intention-to-treat population in patients treated with bevacizumab and radiotherapy (arm A) versus radiotherapy alone (arm B) utilizing the log-rank test. *C:* Deterioration-free survival in the intention-to-treat population in arm A versus arm B. *D:* Individual functional and symptom scores from EORTC QLQ-C30/BN20 modules prior to tumor progression were analyzed in a generalized linear mixed model that controlled for time treatment interactions. Percent effects and 95% confidence intervals are depicted. *E:* Cognitive functioning prior to tumor progression was assessed by mini-mental status examination (MMSE). Boxes define the median and interquartile range, whiskers define the range. Differences in treatment arms were compared by Student's t-test for each timepoint using the Holm-Sidak method to correct for multiple comparisons.

Figure 2. **Molecular glioblastoma subtypes.** *A:* Unsupervised hierarchical clustering by gene methylation patterns. Columns represent patients and rows CpG probes. Pearson's correlation was performed as distance measure and average linkage utilizing the 5,000 probes with highest standard deviations. *B-E:* Progression-free survival *(B, D)* and overall survival *(C, E)* by treatment arm in patients with RTK I gene methylation *(B, C)*, and in patients with PN gene expression *(D, E)* glioblastoma subtypes. One patient with IDH mutated glioblastoma was excluded from outcome analysis in panels *C and E.*

Figure S1. **CONSORT chart.** Abbreviations: BEV, bevacizumab; RT, radiotherapy; MGMT, O^6-methylguanine DNA methyltransferase; PD, progressive disease.

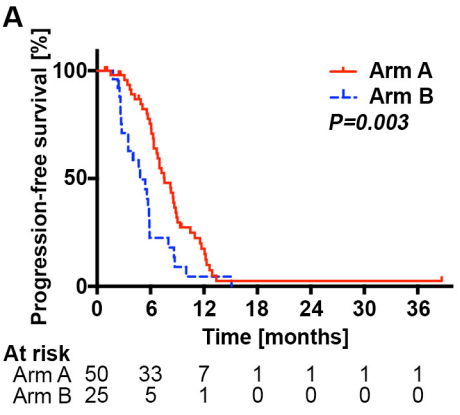
Figure S2. **CONSORT chart of *MGMT* unmethylated patients.** Abbreviations: BEV, bevacizumab; RT, radiotherapy; PD, progressive disease.

Figure S3. **Subgroup analyses of clinical outcomes by treatment arm.** Forest plot depicting univariate hazard ratios and 95% confidence intervals for progression-free survival (left panel) and overall survival (right panel) in arm A versus arm B.

Figure S4. **Clinical outcome by gene methylation subtype.** *A, B:* Progression-free survival (A) and overall survival (B) were analyzed in patients with receptor tyrosine kinase (RTK) I versus RTK II versus mesenchymal (MES) glioblastoma gene methylation subtypes. *C-F:* Progression-free survival (C,E) and overall survival (D,F) were analyzed in patients treated with bevacizumab and radiotherapy (arm A) versus radiotherapy alone (arm B) in subgroups with RTK II (C, D) and MES (E,F) gene methylation. Survival was compared utilizing the log-rank test. The one patient with mutated IDH and an IDH mutation-associated gene methylation pattern was the only patient who survived without progression for >3 years and who was alive and on study treatment at databank closure.

Figure S5. **Clinical outcome by gene expression subtype.** *A, B:* Progression-free survival (A) and overall survival (B) were analyzed in patients with proneural (PN) versus classical (CL) versus mesenchymal (MES) glioblastoma gene expression subtypes. *C-F:* Progression-free survival (C,E) and overall survival (D,F) were analyzed in patients treated with bevacizumab and radiotherapy (arm A) versus radiotherapy alone (arm B) in subgroups with CL (C, D) and MES (E,F) gene expression. Survival was compared utilizing the log-rank test.

Figure 1


A
Progression-free survival [%]
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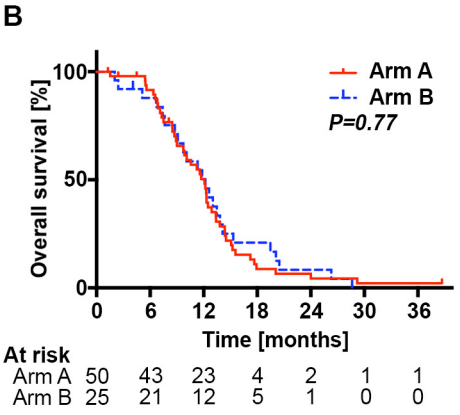
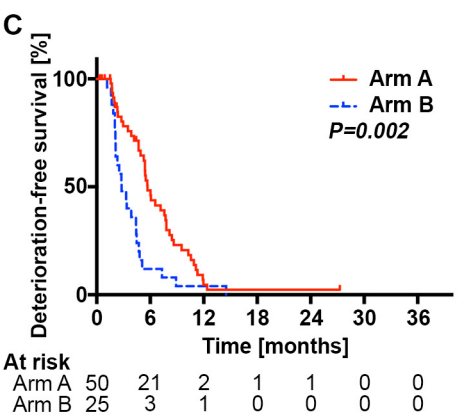
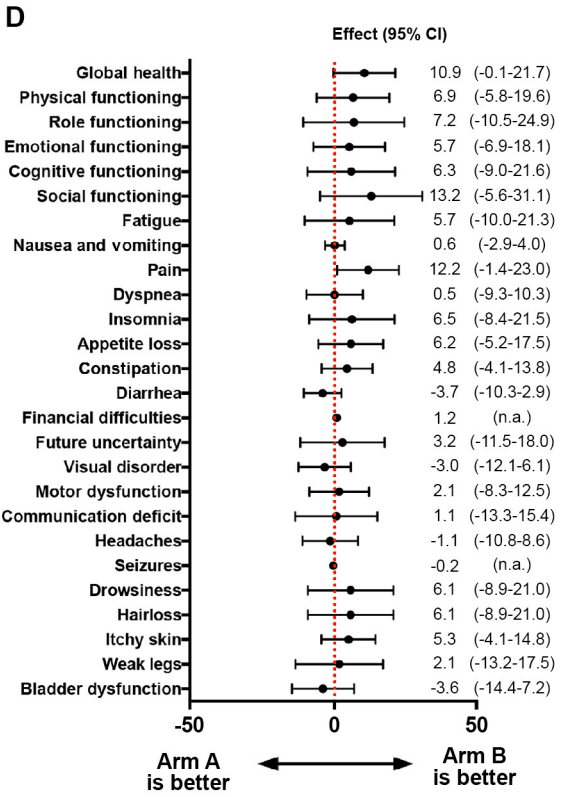
Arm B
P=0.003
0 6 12 18 24 30 36
Time [months]
At risk
Arm A 50 33 7 1 1 1 1
Arm B 25 5 1 0 0 0 0


B
Overall survival [%]
100
50
0
Arm A
Arm B
P=0.77
0 6 12 18 24 30 36
Time [months]
At risk
Arm A 50 43 23 4 2 1 1
Arm B 25 21 12 5 1 0 0


C
Deterioration-free survival [%]
100
50
0
Arm A
Arm B
P=0.002
0 6 12 18 24 30 36
Time [months]
At risk
Arm A 50 21 2 1 1 0 0
Arm B 25 3 1 0 0 0 0


D
Effect (95% CI)
Global health 10.9 (-0.1-21.7)
Physical functioning 6.9 (-5.8-19.6)
Role functioning 7.2 (-10.5-24.9)
Emotional functioning 5.7 (-6.9-18.1)
Cognitive functioning 6.3 (-9.0-21.6)
Social functioning 13.2 (-5.6-31.1)
Fatigue 5.7 (-10.0-21.3)
Nausea and vomiting 0.6 (-2.9-4.0)
Pain 12.2 (-1.4-23.0)
Dyspnea 0.5 (-9.3-10.3)
Insomnia 6.5 (-8.4-21.5)
Appetite loss 6.2 (-5.2-17.5)
Constipation 4.8 (-4.1-13.8)
Diarrhea -3.7 (-10.3-2.9)
Financial difficulties 1.2 (n.a.)
Future uncertainty 3.2 (-11.5-18.0)
Visual disorder -3.0 (-12.1-6.1)
Motor dysfunction 2.1 (-8.3-12.5)
Communication deficit 1.1 (-13.3-15.4)
Headaches -1.1 (-10.8-8.6)
Seizures -0.2 (n.a.)
Drowsiness 6.1 (-8.9-21.0)
Hairloss 6.1 (-8.9-21.0)
Itchy skin 5.3 (-4.1-14.8)
Weak legs 2.1 (-13.2-17.5)
Bladder dysfunction -3.6 (-14.4-7.2)
-50 0 50
Arm A is better
Arm B is better

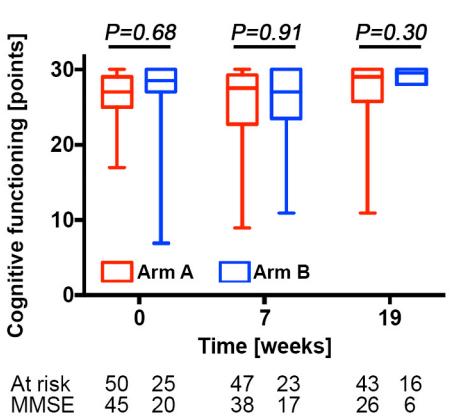
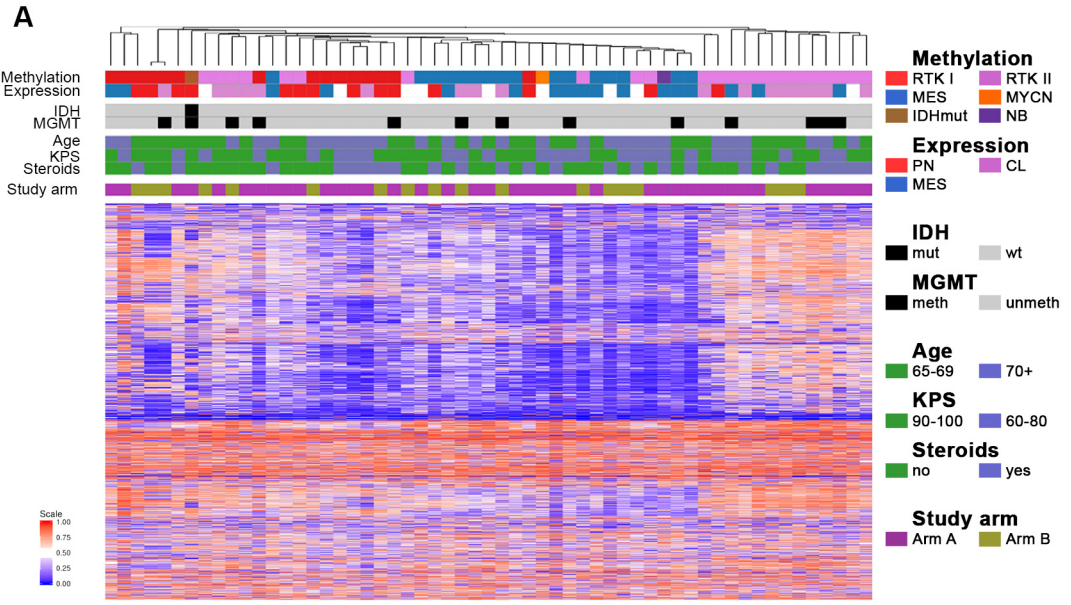
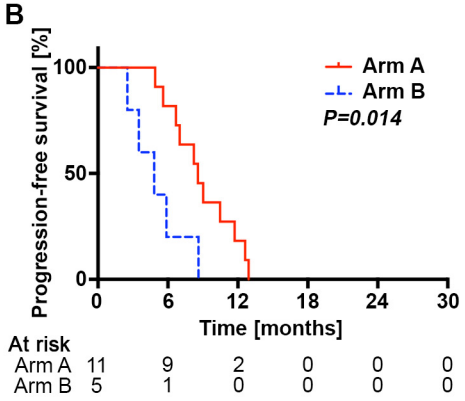
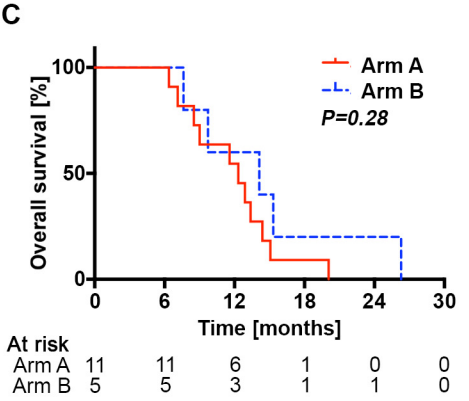
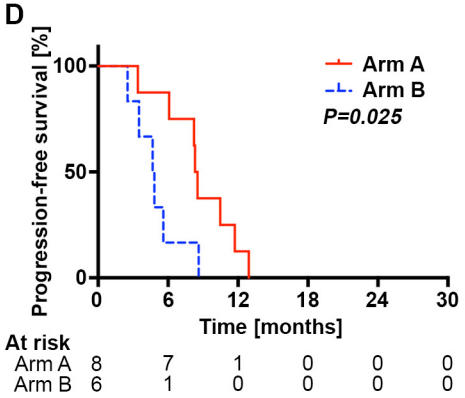

E
Cognitive functioning [points]
30
20
10
0
P=0.68
P=0.91
P=0.30
Arm A
Arm B
0 7 19
Time [weeks]
At risk 50 25 47 23 43 16
MMSE 45 20 38 17 26 6

Figure 2


A
Methylation
Expression
IDH
MGMT
Age
KPS
Steroids
Study arm
Scale
1.00
0.75
0.50
0.25
0.00
Methylation
RTK I
RTK II
MES
MYCN
IDHmut
NB
Expression
PN
CL
MES
IDH
mut
wt
MGMT
meth
unmeth
Age
65-69
70+
KPS
90-100
60-80
Steroids
no
yes
Study arm
Arm A
Arm B


B
Progression-free survival [%]
100
50
0
Arm A
Arm B
P=0.014
0
6
12
18
24
30
Time [months]
At risk
Arm A 11 9 2 0 0 0
Arm B 5 1 0 0 0 0


C
Overall survival [%]
100
50
0
Arm A
Arm B
P=0.28
0
6
12
18
24
30
Time [months]
At risk
Arm A 11 11 6 1 0 0
Arm B 5 5 3 1 1 0


D
Progression-free survival [%]
100
50
0
Arm A
Arm B
P=0.025
0
6
12
18
24
30
Time [months]
At risk
Arm A 8 7 1 0 0 0
Arm B 6 1 0 0 0 0

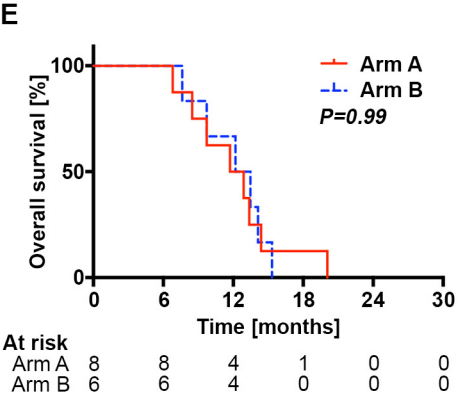

E
Overall survival [%]
100
50
0
Arm A
Arm B
P=0.99
0
6
12
18
24
30
Time [months]
At risk
Arm A 8 8 4 1 0 0
Arm B 6 6 4 0 0 0

Table 1. Patient characteristics.

	Arm A *N=50*	Arm B *N=25*	*P*
Age at diagnosis (years)			
Median	70	70	
Range	65-87	65-79	*0.93*
Gender, N (%)			
Male	32 (64)	16 (64)	
Female	18 (36)	9 (36)	*1.00*
KPS at study entry, N (%)			
90-100	25 (50)	16 (64)	
70-80	21 (42)	6 (24)	
60	4 (8)	3 (12)	*0.30*
MMSE at study entry (points)			
≥ 27	26 (52)	17 (68)	
< 27	19 (38)	3 (12)	*0.032*
No data	5 (10)	5 (20)	
Steroids at study entry, N (%)			
Yes	22 (44)	12 (44)	
No	27 (54)	13 (56)	*0.80*
No data	1 (2)	0 (0)	
CE-T1 (cm^2)			
Median	5.9	3.8	
Range	0.0-32.2	0.5-17.8	*0.12*
Tumor burden on T2 (cm^2)			
Median	15.3	12.1	
Range	2.3-43.2	1.8-39.0	*0.13*
Central histopathology, N (%)			
Glioblastoma	46 (92)	23 (96)	
Anaplastic astrocytoma	1 (2)	0 (0)	
Anaplastic ependymoma	0 (0)	1 (4)	*1.00*
No data	3 (6)	1 (4)	
***IDH*, N (%)**			
Mutated	1 (2)	0 (0)	
Wildtype	39 (78)	19 (76)	*1.00*
No data	10 (20)	6 (24)	
***MGMT* promoter, N (%)**			
Methylated	10 (20)	6 (24)	
Unmethylated	37 (74)	18 (72)	*0.72*
No data	3 (6)	1 (4)	
Gene methylation, N (%)[1]			
RTK I	11 (22)	5 (20)	*0.67*
RTK II	15 (30)	8 (32)	*0.73*
MES	11 (22)	5 (20)	*0.88*
MYCN	1 (2)	0 (0.0)	*n.a.*
IDH mut	1 (2)	0 (0.0)	*n.a.*
No data	11 (22)	7 (28)	*n.a.*
Gene expression, N (%)[2]			
PN	9 (18)	6 (24)	*0.39*
CL	11 (22)	8 (32)	*0.20*

MES	15 (30)	2 (8)	*0.033*
No data	15 (30)	9 (36)	*n.a.*

Abbreviations: CE-T1, contrast enhancement on T1-weighted images; CI, confidence interval; CL, classical; IDH, isocitrate dehydrogenase; KPS, Karnofsky performance score; MMSE, mini-mental status examination; MES, mesenchymal; MGMT, O^6-methylguanine DNA methyltransferase; MYCN, N-myc proto-oncogene; PN, proneural; RTK, receptor tyrosine kinase; [1] Jones et al. 2014 ; [2] Verhaak et al. 2010

Table 2. Multivariate analyses of associations with PFS and OS.

	PFS		**OS**	
	Hazard ratio and 95% CI	***P***	**Hazard ratio and 95% CI**	***P***
Treatment arm: arm A versus arm B	0.36 (0.20-0.65)	*0.001*	1.09 (0.63-1.89)	*0.75*
Age at study entry: 65-69 versus 70+ years	1.13 (0.66-1.92)	*0.651*	0.52 (0.30-0.89)	*0.018*
KPS: 90-100% versus 60-80%	0.50 (0.28-0.89)	*0.018*	0.51 (0.28-0.92)	*0.026*
Steroids at study entry: no versus yes	1.10 (0.66-1.84)	*0.704*	0.87 (0.52-1.44)	*0.59*
MGMT promoter: methylated versus unmethylated*	0.69 (0.37-1.30)	*0.250*	0.79 (0.42-1.49)	*0.46*

* note that enrollment was restricted per amendment 1 to unmethylated patients (see Figure S2)